UNITED STATES PATENT AND TRADEMARK OFFICE

C/C

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/661,927	09/14/2000	William J. Dower	019282-000110US	1158

20350 7590 06/15/2005

TOWNSEND AND TOWNSEND AND CREW, LLP
TWO EMBARCADERO CENTER
EIGHTH FLOOR
SAN FRANCISCO, CA 94111-3834

EXAMINER	
EPPERSON, JON D	
ART UNIT	**PAPER NUMBER**
1639	

DATE MAILED: 06/15/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/661,927	DOWER ET AL.	
	Examiner	Art Unit	
	Jon D. Epperson	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 March 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 3-77* is/are pending in the application.

4a) Of the above claim(s) *See Continuation Sheet* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,14-16,25-35,37,40,46-50,52,53,56,58,66 and 68* is/are rejected.

7)☒ Claim(s) *54* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)

2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3)☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *11/8/04*.

4)☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

5)☐ Notice of Informal Patent Application (PTO-152)

6)☐ Other: _____.

5.0.0

DETAILED ACTION

Status of the Application

1. The Response filed March 3, 2005 is acknowledged.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Status of the Claims

3. Claims 1 and 3-77 were pending. Applicants amended claim 1. No claims were added or canceled. Therefore, claims 1 and 3-77 are currently pending. Claims 4-13, 17-24, 36, 38, 39, 41-45, 51, 55, 57, 59-65, 67 and 69-77 are drawn to non-elected species and/or inventions and thus these claims remain withdrawn from further consideration by the examiner, 37 CFR 1.142(b), there being no allowable generic claim. Therefore, claims 1, 3, 14-16, 25-35, 37, 40, 46-50, 52, 53, 54, 56, 58, 66 and 68 are examined on the merits in this action.

Withdrawn Objections/Rejections

4. All rejections are maintained and the arguments are addressed below.

Outstanding Objections and/or Rejections

Claims Rejections - 35 U.S.C. 102

5. Claims 1, 49, 50, 52, 53, 56, 58, 66 and 68 are rejected under 35 U.S.C. 102(b) as being anticipated by Boyer et al. (Boyer, J. L.; Ananthanarayanan, O. -C.; Hofmann, A. F.; Schteingart,

C. D.; Hagenbuch, B.; Stieger, B.; and Meier, P. J. "Expression and characterization of a functional rat liver Na^+ bile acid cotransport system in Cos-7 cells" *American Journal of Physiology* **1994**, *266(3)*, G382-G387) (of record).

For ***claims 1, 49, 50, 52 and 53***, Boyer et al. (see entire document) disclose screening a functional rat liver Na^+ bile acid cotransport system in Cos-7 cells with a library of fluorescent-conjugated labeled bile acids (e.g., see abstract, "... the transiently transfected COS cells were screened with fluorescent-conjugated labeled bile acids for evidence of expression of the cotransporter"), which anticipates claim 1. For example, Boyer et al. disclose **(a)** providing a library comprising different complexes, each complex comprising a compound and a reporter, the compound varying between different complexes (e.g., see Table 1 wherein Cholyl-Glycyl Fluorescein and Chenodeoxycholyl-Lysyl-NBD are disclosed; in this scenario the "different" compounds are the Cholyl and Chenodeoxycholyl portions and both contain either a Fluorescein or NBD reporter). Boyer et al. also disclose **(b)** providing a population of cells, one or more of which expresses one or more carrier-type transport proteins (e.g., see title wherein COS-7 cells that express the rat liver Na^+ bile acid cotransporter are disclosed; see also page G384, column 2, first paragraph; see also G386, column 2, first full paragraph). Boyer et al. also disclose **(c)** contacting the population of cells with a plurality of complexes from the library (e.g., see Table 1 wherein the measured uptake values are disclosed). Boyer et al. also disclose **(d)** detecting a signal from the reporter of a complex while internalized within a cell (e.g., see figure 2 wherein fluorescent-labeled bile acids are detected in COS-7 cells while said bile acids are internalized; the cells look like this "•" instead of

this "o" and, as a result, the reporter "preferentially" generates the signal once it is internalized within the cell as opposed to complexes binding to the surface of the cell). In addition, fluorescent dyes can be quenched by cell membranes (e.g., see 3/3/05 Response, page 16, paragraph 3, last sentence, "the cell wall and membrane might partially quench the fluorescent ... signal") and, as a result, a different signal would be generated once the dye had entered the cell (e.g., quenched versus non-quenched). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). The Office does not have the facilities to make such a comparison and the burden is on the applicants to establish the difference. See *In re Best,* 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray*, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.). Finally, Boyer et al. disclose that the detected signal provides an "indication" that a complex whose reporter generated the signal comprises a compound that is a substrate for a carrier-type transport protein (e.g., see Table 1; see also pages G383-G384, especially page G384, column 2, paragraph 1, "These findings [referring to the fluorescent signal detection studies] indicate ... the transfected COSS-7 cells expressed ... bile acid transport protein to facilitate specific uptake of these two fluorescent bile acid analogues and that COS-7 cells transfected without the cDNA clone do not contain functional bile cid transport carriers").

For ***claim 56 and 58***, Boyer et al. disclose the "Glycyl" or "Lysyl" linkers or, in the alternative, a "covalent bond" links the compound to the reporter, which is a stable linker lacking a cleavage site.

For ***claim 66***, Boyer et al. disclose Cholyl and Chenodeoxycholyl, which represent small molecules.

For ***claim 68***, Boyer et al. teach the use of controlled cells (e.g., see Boyer et al., figure 1 wherein cells with and without the "insert" are described; see also page G384, column 2, paragraph 1).

Response

6. Applicant's arguments directed to the above 35 U.S.C. § 102 rejection were fully considered (and are incorporated in their entirety herein by reference) but were not deemed persuasive for the following reasons. Please note that the above rejection has been modified from it original version to more clearly address applicants' newly amended and/or added claims and/or arguments.

Applicants argue, "... preferentially generating a signal ... is not referring to the mind of the investigator ... [and] the reporter, preferentially generates a signal (i.e., a greater signal) from internalized complexes relative to complexes bound to the cell surface ... By contrast, Boyer used either a fluorescent or radioactive label. There is no reason to think that either label would generate a preferential signal from within the cell; in fact, one would expect the reverse because the cell wall and membrane might partially quench the fluorescent or radioactive signal from within a cell" (e.g., see 3/3/05 Response, page 16, paragraph 3)

This is not found persuasive for the following reasons:

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., "a greater signal" and "preferential signal") are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Here, Applicants' claims don't require that the signal strength "change" upon internalization (e.g., a "greater" signal). The reporter must preferentially (1) generate the signal once the reporter is internalized within the cell rather than (2) from complexes bound to the surface of the cell. The reason why the signal is generated preferentially inside versus outside (i.e., bound to the surface) is not specified in the claims. Thus, the claims encompass reporters that preferentially generate signals inside the cell because they are preferentially "localized" within the cell as opposed to the surface.

In addition, the Examiner argues that such a signal "increase and/or decrease" (both read on Applicants' claims) would be an inherent feature of the disclosure because the signal generated by a fluorescent dye depends on its environment (e.g., see 3/3/05 Response, page 17, paragraph 3, "the cell wall and membrane might partially quench the fluorescent ... signal") and, as a result, a "different" signal would be generated inside than outside (and/or on the surface) of the cell.

Accordingly, the 35 U.S.C. § 102 rejection cited above is hereby maintained.

Claim Rejections - 35 USC § 103

7. Claims 1, 3, 14-16, 25-35, 37, 40, 46-50, 52, 53, 56, 58, 66 and 68 are rejected under 35 U.S.C. 103(a) as being unpatentable over Boyer et al. (Boyer, J. L.; Ananthanarayanan, O. -C.; Hofmann, A. F.; Schteingart, C. D.; Hagenbuch, B.; Stieger, B.; and Meier, P. J. "Expression and characterization of a functional rat liver Na^+ bile acid cotransport system in Cos-7 cells" *American Journal of Physiology* **1994**, *266(3)*, G382-G387) (of record) and Schaeffer et al. (Schaeffer, J. M.; Hsueh, A. J. W. "α-Bungarotoxin-Luciferin As a Bioluminescent Probe for Characterization of Acetylcholine Receptors in the Central Nervous System" *J. Biol. Chem.* **1984**, *259(4)*, 2055-2058) and Thompson et al. (US Pat. No. 5,824,485) (Date of Patent is **October 20, 1998**) (of record).

For ***claims 1, 49, 50, 52 and 53***, Boyer et al. (see entire document) disclose screening a functional rat liver Na^+ bile acid cotransport system in Cos-7 cells with a library of fluorescent-conjugated labeled bile acids (e.g., see abstract, "... the transiently transfected COS cells were screened with fluorescent-conjugated labeled bile acids for evidence of expression of the cotransporter"), which anticipates claim 1. For example, Boyer et al. disclose **(a)** providing a library comprising different complexes, each complex comprising a compound and a reporter, the compound varying between different complexes (e.g., see Table 1 wherein Cholyl-Glycyl Fluorescein and Chenodeoxycholyl-Lysyl-NBD are disclosed; in this scenario the "different" compounds are the Cholyl and Chenodeoxycholyl portions and both contain either a Fluorescein or NBD reporter). Boyer et al. also disclose **(b)** providing a population of cells, one or more of which expresses one or more carrier-type transport proteins (e.g., see title wherein COS-7 cells

that express the rat liver Na^+ bile acid cotransporter are disclosed; see also page G384, column 2, first paragraph; see also G386, column 2, first full paragraph). Boyer et al. also disclose **(c)** contacting the population of cells with a plurality of complexes from the library (e.g., see Table 1 wherein the measured uptake values are disclosed). Boyer et al. also disclose **(d)** detecting a signal from the reporter of a complex while internalized within a cell (e.g., see figure 2 wherein fluorescent-labeled bile acids are detected in COS-7 cells while said bile acids are internalized). The requirement that the reporter "preferentially generate the signal once the reporter is internalized within the cell" has not been given any patentable weight because the use of the term "preferential" has broadly been interpreted to be an "optional" method step that is ultimately determined by the investigator (i.e., it is "preferential" to the investigator or "not required"). Finally, Boyer et al. disclose that the detected signal provides an "indication" that a complex whose reporter generated the signal comprises a compound that is a substrate for a carrier-type transport protein (e.g., see Table 1; see also pages G383-G384, especially page G384, column 2, paragraph 1, "These findings [referring to the fluorescent signal detection studies] indicate ... the transfected COSS-7 cells expressed ... bile acid transport protein to facilitate specific uptake of these two fluorescent bile acid analogues and that COS-7 cells transfected without the cDNA clone do not contain functional bile cid transport carriers").

For ***claim 26***, Boyer et al. teach the use of controlled cells (e.g., see Boyer et al., figure 1 wherein cells with and without the "insert" are described).

For ***claim 37***, Boyer et al. disclose the use of different reporters including fluorescent labels (e.g., see Table I, wherein Fluorescein and NBD are disclosed).

For ***claim 47***, Boyer et al. disclose a population of cells that have been transformed with a DNA library encoding the one or more transport proteins (e.g., see figure 1 showing DNA "insert" for transporter).

For ***claim 56 and 58***, Boyer et al. disclose the "Glycyl" or "Lysyl" linkers or, in the alternative, a "covalent bond" links the compound to the reporter, which is a stable linker lacking a cleavage site.

For ***claim 66***, Boyer et al. disclose Cholyl and Chenodeoxycholyl, which represent small molecules.

For ***claim 68***, Boyer et al. teach the use of controlled cells (e.g., see Boyer et al., figure 1 wherein cells with and without the "insert" are described; see also page G384, column 2, paragraph 1).

The prior art teaching of Boyer et al. differ from the claimed invention as follows:

For ***claim 3***, Boyer et al. fail to teach a reporter with a cleavable site.

For ***claims 14-16***, Boyer et al. fail to teach a reporter comprising a substrate for an enzyme wherein the enzyme.

For ***claims 25, 27 and 35***, Boyer et al. fail to teach contacting a plurality of different complexes with different cells in a single reaction vessel or different cells in separate reaction vessels.

For ***claims 28-34, 40***, Boyer et al. fail to teach cells with different characteristics e.g., morphology, etc.

For ***claim 46***, Boyer et al. fail to teach the use of a "focused" library.

For ***claim 48***, Boyer et al. fail to teach the "isolation" of unknown transporter compounds. The transporter in Boyer et al. was known and thus did not need to be isolated.

However, the combined references of Schaeffer et al. and Thompson et al. teach the following limitations that are deficient in Boyer et al.:

For ***claim 3, 14-16***, the combined references of Schaeffer et al. and Thompson et al. (see entire documents) teach the use of luciferin conjugates (which are substrates for the enzyme luciferase) within a cell to produce upon enzymatic cleavage a detectable signal (e.g., see Schaeffer et al., abstract; see also Thompson et al., column 22, line 25; see also column 36, line 23; see also section 5.2.2.). Please note that these reporters would "preferentially" generate a signal after being internalized within the cell.

For ***claims 25, 27 and 35***, the combined references of Schaeffer et al. and Thompson et al. teach different screening formats with populations of different cells in single and/or different containers (see Thompson et al., column 34, line 32; see also column 28, line 57; see generally section 5.2).

For ***claims 28-34, 40***, the combined references of Schaeffer et al. and Thompson et al. teach different characteristics including different stains, epitopes, etc. (see section 5.2.3; see column 30, line 50; see also column 29, line 51; see also column 10, paragraph 2; see also column 10, last paragraph; column 38, line 64; column 32, line 63).

For ***claim 46***, the combined references of Schaeffer et al. and Thompson et al. teach the use of a focused library (e.g., see Thompson et al., column 32, lines 15-16; see section 5.2.3).

For ***claim 48***, the combined references of Schaeffer et al. and Thompson et al. disclose the "isolation" of unknown expression products using HTS techniques (e.g., Thompson et al., column 5, lines 64-65).

It would have been obvious to one skilled in the art at the time the invention was made to use the screening method as taught by Boyer et al. with the luciferin conjugates as taught by the combined teachings of Schaeffer et al. and Thompson et al. because Schaefer et al. and Thompson et al. generally teach that luciferin conjugates can be broadly applied to a wide range of screening systems (e.g., see Schaefer et al., paragraph bridging pages 2057-2058, "future conjugations of luciferin to various other ligands will provide the basis for the development of sensitive bioluminescent immunoassays and bioluminescent ligand receptor assays"). Furthermore, a person of skill in the art would readily recognize that the problem of visualizing molecules using a fluorescent probe is not "unique" to the system set forth by Boyer et al. (e.g., see *In re Paulsen* 31 USPQ2d 1671 (Fed. Cir. 1994) (A "clam style" fastening means is not "unique" to the computer industry and, as a result, a person of skill would consult other "mechanical" literature for a solution to this fastening problem including literature that does not encompass computers). Thus, a person of skill in the art would readily consult other "fluorescent assays and/or screening" literature that use such fluorescent probes (e.g., Schaeffer et al.

and Thompson et al.) for the purpose of finding safer, faster, more sensitive, etc. probes (i.e., the references represent analogous art in conformity with *In re Paulsen*).

Here, a person of skill in the art would have been motivated to use the luciferin conjugates because of their high sensitivity (e.g., see Schaeffer et al., abstract), high stability to proteolytic enzyme degradation within the cell, and small size that would be more amenable to transport (e.g., see Schaeffer et al., page 2057, column 2, paragraph 1). In addition, Thompson et al. also demonstrate that luciferin/luciferase reporter systems can be successfully applied to high throughput cell based assays (e.g., see Thompson et al., column 22, line 25; see also column 36, line 23), which would increase the screening output of the technique disclosed by Boyer et al. Furthermore, Thompson et al. indicate that the teachings of Boyer et al. could be expanded using luciferein/luciferase reporter systems in a greater number of organisms that do not grow very well (e.g., see Thompson et al, column 12, lines 55-57; see also column 24, last paragraph wherein the use of carrier type transport proteins like mdr1 are disclosed), which would increase the variety of transporters that could be screened. Finally, a person of skill in the art would have reasonably been expected to be successful because Schaeffer et al. explicitly state that the luciferin conjugates can be generally applied to a wide range of systems (see above) and are resistant to proteolytic degradation within the cell, which are similar conditions to those encountered by Boyer et al. Furthermore, the small size of luciferin would be less likely to interfere with the uptake of the probe conjugate by the transporter.

Response

8. Applicant's arguments directed to the above 35 U.S.C. § 103(a) rejection were fully considered (and are incorporated in their entirety herein by reference) but were not deemed persuasive for the following reasons. Please note that the above rejection has been modified from it original version to more clearly address applicants' newly amended and/or added claims and/or arguments.

[1] Applicants argue, "none of the motivation alleged by the Office Action would have impelled the artisan to the specific combination claimed ... Schaeffer ... refers to development of immunoassays and bioluminescent ligand-receptor assays ... [which] provide no indication of other assays in which either luciferin or luciferase might be used" (e.g., see 3/3/05 response, pages 17-18).

[2] Applicants argue, "The only asserted motivation for combining Thompson with Boyer is the passage at col. 12, lines 55-57." (e.g., see 3/3/05 Response, page 18, middle paragraph).

[3] Applicants argue, "[The cited passage in the rejection] does not indicate that Thompson's method could or should be used to analyze transporters, much less in the manner claimed" (e.g., see 3/3/05 Response, page 18, middle paragraph).

[4] Applicants argue, "Schaeffer does not say that luciferin conjugates can be generally applied to a wide range of systems but rather says thy can be used for detection of a broad range of ligands in immunoassay or ligand receptor assays ... Likewise ... Thompson['s] ... high throughput assays is not predictive of the claimed methods" (e.g., see 3/3/05 Response, page 18, last full paragraph).

[5] Applicants argue, "In Thompson's method, DNA encoding luciferase in introduced into a cell in a vector. Such does not suggest or predict the success of introducing luciferin as a molecule linked to a compound, as a means of monitoring passage of the compound into the cell" (e.g., see 3/3/05 Response, page 18, last full paragraph).

[6] Applicants argue with regard to dependent claims 25, 27, 28-35, 40 and 56, "No reason has been provided that the artisan would have seen [1] any connection between whether Thompson does or does not mix cells in the generation and screening of shuffled gene libraries with whether mixtures of cells should be used in screening compounds for capacity to be transported into cells ... [2] any relevance of the use of diverse strains for gene shuffling with the use of different strains to allow multiple transport assays to be conducted simultaneously in the same vessel ... [3] any connection between such teaching and methods employing variants of a compound in assays for a substrate of a transporter (e.g., see 3/3/05 Response, pages 19-20).

[7] Applicants argue that a person of skill in the art would not have been motivated to and/or known how to modify the teachings of Boyer from a method of identifying a substrate of a known transporter into a method of identifying a hitherto unknown transporter for a known compound and cite Standard Oil Co. in support of this position (e.g., see 3/3/05 Response, page 20).

This is not found persuasive for the following reasons:

[1] In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the

knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). Here, a person of skill in the art would have been motivated to use the luciferin conjugates because of their high sensitivity (e.g., see Schaeffer et al., abstract), high stability to proteolytic enzyme degradation within the cell, and small size that would be more amenable to transport (e.g., see Schaeffer et al., page 2057, column 2, paragraph 1). In addition, Thompson et al. also demonstrate that luciferin/luciferase reporter systems can be successfully applied to high throughput cell based assays (e.g., see Thompson et al., column 22, line 25; see also column 36, line 23), which would increase the screening output of the technique disclosed by Boyer et al. Furthermore, Thompson et al. indicate that the teachings of Boyer et al. could be expanded using luciferein/luciferase reporter systems in a greater number of organisms that do not grow very well (e.g., see Thompson et al, column 12, lines 55-57; see also column 24, last paragraph wherein the use of carrier type transport proteins like mdr1 are disclosed), which would increase the variety of transporters that could be screened.

To the extent that Applicants are arguing that Schaeffer et al. and Boyer et al. are not "analogous" art, the Examiner contends that a person of skill in the art would readily recognize that the problem of visualizing molecules using a fluorescent probe is not "unique" to the system set forth by Boyer et al. in accordance with *In re Paulsen* (e.g., see *In re Paulsen* 31 USPQ2d 1671 (Fed. Cir. 1994) (A "clam style" fastening means is not "unique" to the computer industry and, as a result, a person of skill would consult other "mechanical" literature for a solution to this fastening problem). Here, a person of skill in the art would readily consult other "fluorescent assays and/or screening" literature that use such fluorescent probes (such as Schaeffer et al. and

Thompson et al.) for the purpose of finding safer, faster, more sensitive, etc. probes (i.e., the references represent analogous art in conformity with *In re Paulsen*).

[2] The Examiner respectfully disagrees. For example, Thompson et al. state that luciferin/luciferase can be used in a high throughput screening (HTS) (e.g., see Thompson et al., column 22, line 25; see also column 36, line 23). The strongest rationale for combining references is a recognition, expressly or impliedly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent, that some advantage or expected beneficial result would have been produced by their combination. *In re Sernaker*, 702 F.2d 989, 994-95, 217 USPQ 1, 5-6 (Fed. Cir. 1983). Here, the beneficial result is "speed" brought about by the HTS format that the luciferin/luciferase system permits (i.e., the method of Boyer et al. would be faster when combined with the combined teachings of Thompson et al. (and Schaeffer et al.).

[3] The Examiner respectfully disagrees. Thompson et al. disclose the use of carrier-type transporter proteins such as mdr1 (e.g., see column 24, last paragraph). In addition, please note, "... there is no requirement that the prior art provide the same reason as the applicant to make the claimed invention", see MPEP § 2144"). Thus, a motivation to practice the teachings of Boyer et al. on a greater number of organisms when combined with the teachings of Thompson et al. (and Schaeffer et al.) is consistent with MPEP § 2144.

[4] To the extent that Applicants are arguing that Schaeffer et al. and Boyer et al. (and/or Thompson et al.) are not "analogous" art, the Examiner contends that a person of skill in the art would readily recognize that the problem of visualizing molecules using a fluorescent probe is not "unique" to the system set forth by Boyer et al. in accordance with *In re Paulsen* (e.g., see *In*

re Paulsen 31 USPQ2d 1671 (Fed. Cir. 1994) (A "clam style" fastening means is not "unique" to the computer industry and, as a result, a person of skill would consult other "mechanical" literature for a solution to this fastening problem). Here, a person of skill in the art would readily consult other "fluorescent assays and/or screening" literature that use such fluorescent probes (such as Schaeffer et al. and Thompson et al.) for the purpose of finding safer, faster, more sensitive, etc. probes (i.e., the references represent analogous art in conformity with *In re Paulsen*).

[5] In response to applicant's arguments against the Thompson et al. reference individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See In re Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); In re Merck & Co., 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Here, the combined teachings set forth a luciferin molecule linked to a compound (e.g., see Schaeffer) and a means of monitoring passage of a compound into a cell (e.g., see Boyer et al.).

[6] The Examiner argues that no such "connection" is required (e.g., see MPEP § 2144, "there is no requirement that the prior art provide the same reason as the applicant to make the claimed invention").

[7] The Examiner respectfully disagrees with Applicants' assessment of this quotation. Judge Rich (in *Standard Oil Co.*) was merely using this quotation to demonstrate the test for obviousness as set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966) requiring that a determination of the level of ordinary skill in the art should be based on a "hypothetical" person having "ordinary skill in the art", not the "actual" skill of the Applicant. Thus, the quoted statement merely defines what "ordinary skill in the art" means (e.g., it is not

based on the "actual" skill of an inventor that might depart from the "conventional wisdom" of a "hypothetical" person). Here, the Examiner has never asserted that the ordinary skill should be based on Applicants' own knowledge "non-conventional wisdom" and, as a result, S*tandard Oil Co.* as outlined by Applicants does not apply. Furthermore, even if *assuming arguendo* that *Standard Oil Co.* does apply, the combined teachings of Schaeffer et al. and Thompson et al. clearly represent what was "conventional" in the art at the time of filing and thus modification of the Boyer et al. reference is appropriate in accordance with Graham v. John Deer Co. and section 35 U.S.C. § 103(a).

Accordingly, the 35 U.S.C. § 103(a) rejection cited above is hereby maintained.

New Rejections

Claims Rejections - 35 U.S.C. 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claims 1, 49, 50 and 66 are rejected under 35 U.S.C. 102(b) as being anticipated by Schramm et al. (Schramm U.; Dietrich, A.; Schneider, S.; Buscher, H. P.; Gerok, W.; Kurz, G. "Fluorescent derivatives of bile salts. II. Suitability of NBD-amino derivatives of bile salts for the study of biological transport" *Journal of Lipid Research* **1991**, *32*, 1769-1779).

For ***claim 1***, Schramm et al. (see entire document) disclose methods for using a library of fluorescent derivatives of bile salts (see Schramm et al., abstract), which

anticipates the claimed invention. For example, Schramm et al. disclose providing a library comprising different complexes, each complex comprising a compound and a reporter, the compound varying between different complexes (e.g., see abstract wherein a library unconjugated and taurine-conjugated NBD-amino-dihydroxy-5β-cholan-24-oic acids bearing a fluorophor in the 3α, 3β, 7α, 7β, 12α or 12β positions are disclosed. In this scenario, the NBD represents the reporter and the 3α, 3β, 7α, 7β, 12α and 12β isomers of the unconjugated and taurine-conjugated bile salts represent the library). Schramm et al. further disclose providing a population of cells, one or more of which expresses one or more carrier-type transport proteins (e.g., see page 1777, column 1, last full paragraph, wherein rat hepatocytes are disclosed as the population of cells that express bile acid transporters; see also figure 9a showing uptake of 7β-NBD-NCT; see also specification, figures 22-25 wherein the rat bile acid transporter is disclosed as a carrier mediated transporter; see also definition section, "Some examples of transporter proteins effecting carrier-mediated transport ... [include] bile acid transporter"). Schramm et al. disclose contacting the population of cells with a plurality of complexes from the library (e.g., abstract wherein both NBD-NC and NBD-NCT isomers were contacted with rat hepatocytes; see also Materials and Methods, Liver infusion experiments and Isolation of hepatocytes sections; see also Results, Metabolism and secretion sections for both unconjugated and conjugated bile acids). Finally, Schramm et al. disclose detecting a signal from the reporter of a complex while internalized within a cell (e.g., see figure 9a wherein a signal is detected for the internalized 7β-NBD-NCT; see also page 1775, Visualization of transport in rat liver section; see also page 1777,

column 2, first full paragraph, "7α-NBC-NC and 7β-NBD-NC may be used ... for the study of hepatobilary transport of unconjugated bile salts by fluorescence microscopy"). Schramm et al. also disclose a reporter that preferentially generates the signal once the reporter is internalized within the cell rather than from complexes binding to the surface of the cell (e.g., see figure 9a, showing the signal being generated predominantly from the internal portions of the cell as opposed to the cell periphery or surface (i.e., the cells look like this "•" instead of this "○" as a result of the "localization" of the dye within the cell instead of at its membrane; in addition, the wavelength maximum and the emission intensity also change when the 7β-NBD-NCT is internalized within the cell because the 7β-NBD-NCT is sensitive to its environment as exemplified in figure 1 and Table 1 and, as a result, a "new" signal is generated upon internalization of the dye). Boyer et al. also disclose that the detected signal provides an "indication" that a complex whose reporter generated the signal comprises a compound that is a substrate for a carrier-type transport protein (e.g., see figure 9a showing uptake).

For ***claims 49-50***, Schramm et al. disclose rat "liver bile acid" transporters (e.g., see abstract; see also figure 9a; see also Materials and Methods).

For ***claim 66***, Schramm et al. disclose bile acid small molecules (e.g., see abstract).

Conclusion

Applicant's amendment necessitated any new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO

MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon D Epperson whose telephone number is (571) 272-0808. The examiner can normally be reached Monday-Friday from 9:00 to 5:30.

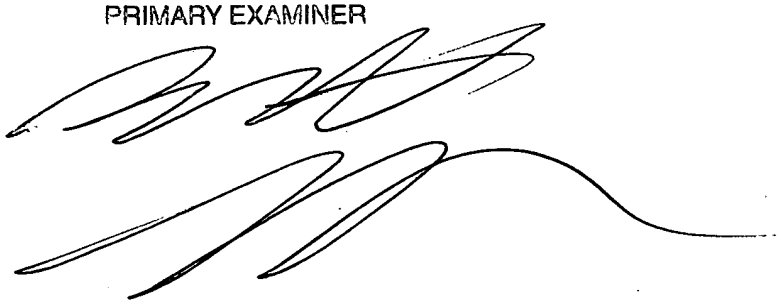
If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on (571) 272-0811. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jon D. Epperson, Ph.D.
June 5, 2005

BENNETT CELSA
PRIMARY EXAMINER



Continuation of Disposition of Claims: Claims withdrawn from consideration are 4-13,17-24,36,38,39,41-45,51,55,57,59-65,67 and 69-77.